Compstatin Cp40 blocks hematin-mediated deposition of C3b fragments on erythrocytes: Implications for treatment of malarial anemia

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About the research

A central question in the pathogenesis of malarial anemia focuses on the mechanisms of destruction of erythrocytes (E), because for every E destroyed due to infection by the causative parasite, Plasmodium falciparum (Pf), 20 uninfected E are cleared from the bloodstream. An increasing body of evidence indicates that the alternative pathway of the human complement system is activated during malarial infections, due to generation of several inflammatory agents that are produced when Pf-infected E are destroyed. As a consequence, uninfected E are targeted by complement, ultimately leading to their clearance from the bloodstream. We hypothesize that the same mechanism reported by Prof. Antonio Risitano for loss of E that occurs in individuals with paroxysmal nocturnal hemoglobinuria (PNH) who receive eculizumab (anti-C5 therapy) will also obtain for malarial anemia. We reported that mAb 3E7 could be used to block the alternative pathway, but use of this agent to treat malarial anemia is quite problematic due to several technical issues including cost. Prof. John Lambris has developed a small molecule peptide inhibitor of complement, Compstatin, which may find use in several indications including PNH. In this manuscript, in collaboration with Profs. Lambris and

Risitano, we demonstrate that in our model system Compstatin can indeed block complement activation and targeting of uninfected E mediated by inflammatory products that are produced due to destruction of Pf-infected E. We hope that in the future this reagent, which can be administered easily and at very low cost, will find use in the treatment or prevention of malarial anemia.

About the authors

Professors Ronald Taylor and Margaret Lindorfer, at the University of Virginia School of Medicine, are both trained as chemists, and received their Ph.D.s at Princeton University and the University of Oregon, respectively. They are pleased to have the opportunity to collaborate with their friends and colleagues, Professors Antonio Risitano (Federico II University of Naples) and John Lambris (University of Pennsylvania).